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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,057	01/28/2004	Roy H. Larsen	50147/003002	2306

21559 7590 11/26/2007

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EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	**PAPER NUMBER**
1618	

NOTIFICATION DATE	DELIVERY MODE
11/26/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/766,057	LARSEN ET AL.	
	Examiner	Art Unit	
	Melissa Perreira	1618	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18 and 25-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18 and 25-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/10/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/10/07 has been entered.

Claims and Previous Rejections Status

Claims 18 and 25-35 are pending in the application.

The rejection under 35 U.S.C. 102(b) as being anticipated by Niswender (US 4,336,185) is withdrawn.

The rejections under 35 U.S.C. 103(a) as being unpatentable over Niswender (US 4,336,185) in view of Goldenberg et al. (US 5,698,178) and Wedeking et al. (US 6,093,382) and as being unpatentable over Sinkule et al. (EP 282057) in view of Wedeking et al. (US 6,093,382) have been modified.

The rejection on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. US 6,740,304B2 is maintained.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 18 and 25- 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niswender (US 4,336,185) in view of Wedeking et al. (US 6,093,382) and further in view of Sinkule et al. (EP 282057).

3. Niswender (US 4,336,185) discloses a receptor binding conjugate that may comprise three components, 1.) folic acid and salts, esters, and amides thereof and an antibody, such as a gamma globulin (as evidenced by Wikipedia and not excluding human) and/or a radionuclide or radionuclides (column 1, lines 17-62). The conjugates of the disclosure may competitively bind with folic acid binding proteins or an antibody in a vertebrate by an antigenic protein conjugate of folic acid (column 2, lines 1-4). Niswender does not disclose the antibody to be human IgG or the method of targeting a radionuclide to a malignant cell within a subject.

4. Wedeking et al. (US 6,093,382) discloses the gadolinium-folate (folic acid) conjugates (column 7, lines 21-28; column 8, line 56; column 10, lines 18-25) that are used to target the radionuclide to tumor cells via FBP (folate binding protein) and their methods or preparation and use (column 6, lines 28+; column 7, lines 48-50). The compound of column 51-52 contains multiple folates (folic acid) conjugated to a radionuclide chelate capable of binding gadolinium. The method of targeting a

gadolinium-folate (folic acid) conjugate to a cell involves administering to a mammal the conjugate and monitoring the biodistribution (column 68, lines 31+; example 17). Also disclosed is that cellular uptake of folate into cells is via a high affinity membrane bound folate-binding protein and it is transported into the cell and diffuses into the cytoplasm where it is rapidly coupled to one or more glutamic acid residues thus slowing diffusion out of the cell (column 3, lines 3-24). Due to the overexpression of folate binding protein in cancer cells (column 3, lines 34-35; column 4, lines 42-43) it would be obvious that the targeting of a radionuclide would be enhanced by conjugation to folic acid (column 5, lines 1-7).

5. Sinkule et al. (EP 282057) discloses a receptor binding conjugate comprising three components, 1.) a monoclonal antibody (column 2, lines 30-31), 2.) a radionuclide and 3.) a chemotherapeutic agent, such as folate or analogues thereof (abstract; column 2, lines 11-14 and 29-30) or multiples thereof (column 4, lines 18-28) which are prepared by attaching a radionuclide to a conjugate comprising an antibody and a therapeutic agent (column 6, lines 22-25). The antibody may be a monoclonal or polyclonal or variations thereof used for a wide variety of target antigens (column 3, lines 56+; column 4, lines 9-12). Various radionuclides are disclosed, such as ^{125}I, ^{99m}Tc or others encompassed by the instant claims (column 3, lines 39+) and may be bound to the antibody-therapeutic agent conjugate via a chelating compound (column 17, lines 5-17). Targeting antibodies may be included in the conjugate to target the conjugate to a desired tumor cell for uptake via administration to a mammalian host (column 5, lines 10-12 and 22+; column 6, lines 26-30). The antibodies disclosed for

conjugating to a radionuclide-chemotherapeutic agent include IgG, such as 443A6 which recognize a 40k dalton epithelial antigen found on human breast adenocarcinomas (column 8, lines 33-39; example 3). The therapeutic agent chosen for use will vary according to the nature of the disease to be treated and the type of target cells to be eradicated *in vivo* within human or mammalian host (column 3, lines 5-12; column 5, lines 22-25). The conjugate can be administered by any conventional method, such as intravenously and the pharmaceutical agents may be in various pharmaceutical compositions with various combinations of materials therefore. The method of preparing the folic acid derivative-antibody bond involves conversion of the folic acid derivative to the activated ester (mixed anhydride) with acetic anhydride (column 8, lines 40-44).

6. At the time of the invention it would be obvious to one ordinarily skilled in the art to substitute the antibodies of Sinkule et al. for those of Niswender to be used for site-selectivity of a wide variety of target antigens and thus target a conjugate into a cell with enhanced affinity. Folic acid is a known vitamin that can provide nutrients into a subject. It is obvious to substitute variants of similar structure in order to generate the most efficient and effective diagnostic and/or therapeutic agent. It would also be obvious to one ordinarily skilled in the art to utilize the conjugates of the combined disclosure for the method of Wedeking et al. and Sinkule et al. for targeting a gadolinium-folate (folic acid)-antibody conjugate to a cell states as Sinkule et al. describes targeting antibodies may be included in the conjugate to target the conjugate to a desired tumor cell for uptake via administration to a mammalian host (Sinkule et al.,

column 5, lines 10-12 and 22+; column 6, lines 26-30). Folate has a high cellular uptake into cells via a high affinity membrane bound folate-binding protein, is transported into the cell and diffuses into the cytoplasm where it is rapidly coupled to one or more glutamic acid residues thus slowing diffusion out of the cell. Due to the overexpression of folate binding protein in cancer cells it would be obvious that the targeting of a radionuclide would be enhanced by conjugation to folic acid (as stated above).

7. Claims 18,25-28 and 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niswender (US 4,336,185) in view of Wedeking et al. (US 6,093,382) and further in view of Goldenberg et al. (US 5,698,178).

8. Niswender (US 4,336,185) discloses a receptor binding conjugate that may comprise three components, 1.) folic acid and salts, esters, and amides thereof and an antibody, such as a gamma globulin (as evidenced by Wikipedia and not excluding human) and/or a radionuclide or radionuclides (column 1, lines 17-62). The conjugates of the disclosure may competitively bind with folic acid binding proteins or an antibody in a vertebrate by an antigenic protein conjugate of folic acid (column 2, lines 1-4). Niswender does not disclose the antibody to be human IgG or the method of targeting a radionuclide to a malignant cell within a subject.

9. Wedeking et al. (US 6,093,382) discloses the gadolinium-folate (folic acid) conjugates (column 7, lines 21-28; column 8, line 56; column 10, lines 18-25) that are

used to target the radionuclide to tumor cells via FBP (folate binding protein) and their methods or preparation/use as well as that stated above.

10. Goldenberg et al. (US 5,698,178) discloses the method of selectively targeting diagnostic and therapeutic agents to multidrug resistant cells via administration of receptor binding conjugates (column 4, lines 1-4; column 5, line 56; column 23, lines 1-3). The receptor binding conjugates comprise various antibodies and at least one diagnostic or therapeutic agent (abstract, column 4, lines 8-26). The diagnostic and therapeutic agents include radionuclides, such as ^{25}I, ^{99m}Tc, etc. (column 20, lines 39-53) and cancer chemotherapeutic drugs, such as folic acid analogues (column 4, lines 44 and 55; column 23, lines 11+ and lines 55-57). Humanized antibodies may be used as an equivalent to other antibodies for targeting a desired site and that the use of humanized antibodies obviates potential problems associated with the immunogenicity of murine constant regions (column 10, line 17+; column 12, lines 4-13). Antibodies that may be used as the targeting antibody which provides for the clearance of a nontargeted circulating radiolabeled antibody are IgG and IgM (column 20, lines 54+). The method of preparing the conjugates involves coupling an antibody to a diagnostic or therapeutic agent (column 15, lines 43-45; example 4).

11. At the time of the invention it would be obvious to one ordinarily skilled in the art to substitute the antibodies of Goldenberg et al. for those of Niswender to be used for site-selectivity of a wide variety of target antigens and thus target a conjugate into a cell with enhanced affinity. Folic acid is a known vitamin that can provide nutrients into a subject. It is obvious to substitute variants of similar structure in order to generate the

most efficient and effective diagnostic and/or therapeutic agent. It would also be obvious to one ordinarily skilled in the art to utilize the conjugates of the combined disclosures for the method of Wedeking et al. for targeting a gadolinium-folate (folic acid)-antibody conjugate to a cell states as Wedeking et al. states that folate analogues may be used. Folate has a high cellular uptake into cells via a high affinity membrane bound folate-binding protein, is transported into the cell and diffuses into the cytoplasm where it is rapidly coupled to one or more glutamic acid residues thus slowing diffusion out of the cell. Due to the overexpression of folate binding protein in cancer cells it would be obvious that the targeting of a radionuclide would be enhanced by conjugation to folic acid (as stated above).

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 18,25-28 and 31-35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. US 6,740,304B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of delivering therapeutic radiation to a patient with a malignant cell of US 6,740,304B2 encompasses the method of targeting a radionuclide to a malignant cell within a subject of the instant claims. The methods involve identical conjugates comprising a human IgG or IgM antibody (not excluding inert antibodies), folate (not excluding multiple folates) and a radionuclide. The species of administration techniques, such as intravenously of US 6,740,304B2 anticipates the genus of administration of the instant claims. The cells to target or deliver the radionuclide are brain, cervical, ovarian, or breast and the species of radionuclides, such as ^{125}I of US 6,740,304B2 anticipates the genus or radionuclide of the instant claims.

Response to Arguments

14. In regards to the rejection under 35 U.S.C. 103(a) as being unpatentable over Niswender (US 4,336,185) in view of Wedeking et al. (US 6,093,382) and further in view of Sinkule et al. (EP 282057).

15. Applicant asserts that the folate analogues of Sinkule et al. are examples of chemotherapeutic agents but these are not true folates as they are cytotoxic.

16. The reference of Sinkule et al. was not used to teach of non-cytotoxic folate but was used to teach that radionuclide-folate analogue-antibody constructs may contain antibodies IgG, such as 443A6. The reference of Niswender was used to teach of a receptor binding conjugate that may comprise three components, 1.) folic acid and salts, esters, and amides thereof (non-cytotoxic) and an antibody, such as a gamma globulin (as evidenced by Wikipedia and not excluding human) and/or a radionuclide or radionuclides (column 1, lines 17-62). The folic acid salts of Niswender encompass those of the instant claims and are therefore non-cytotoxic. It would be obvious and predictable to substitute the antibodies of Sinkule et al. for those of Niswender to alter the site-selectivity of a wide variety of target antigens and thus target a conjugate into a cell with enhanced affinity.

17. Applicant asserts that Wedeking et al. does not indicate any advantages in the use of a dual-targeting conjugate with two separate tumor-binding components.

18. Wedeking et al. teaches that due to the overexpression of folate binding protein in cancer cells (column 3, lines 34-35; column 4, lines 42-43) it would be obvious that the targeting of a radionuclide would be enhanced by conjugation to folic acid while Sinkule et al. teaches that the antibodies disclosed for conjugating to a radionuclide-chemotherapeutic agent include IgG, such as 443A6 recognize a 40k dalton epithelial antigen found on human breast adenocarcinomas. In combination, it would be obvious that a dual-targeting conjugate is advantageous to selectively bind the conjugates to cancer cells (which most overexpress) and in particular to human breast adenocarcinomas.

19. In regards to the rejection under 35 U.S.C. 103(a) as being unpatentable over Niswender (US 4,336,185) in view of Wedeking et al. (US 6,093,382) and further in view of Goldenberg et al. (US 5,698,178).

20. Applicant asserts that Niswender does not describe a conjugate containing a radionuclide at least one non-cytotoxic folate and an *antibody, antibody fragment or antibody construct.*

21. Niswender does disclose a receptor binding conjugate that may comprise three components, 1.) folic acid and salts, esters, and amides thereof and an antibody, such as a gamma globulin (as evidenced by Wikipedia and not excluding human) and/or a radionuclide or radionuclides (column 1, lines 17-62).

22. Applicant asserts that Goldenberg et al. teaches of folic acid analogs which are chemotherapeutic agents and are toxins that kill cells.

23. Goldenberg et al. was not used to teach of the non-cytotoxic folate but that the substitution of the antibodies of Goldenberg et al. for those of Niswender would be used for site-selectivity of a wide variety of target antigens and thus target a conjugate into a cell with enhanced affinity. It would be obvious and predictable to substitute one antibody for another to alter the site-selectivity.

24. Applicant asserts that Wedeking et al. provides not teaching or suggesting to use a conjugate containing a non-cytotoxic folate and an antibody or antibody fragment to target a tumor associated antigen.

25. The combined references of Niswender and Goldenberg et al. provide for the conjugate containing a non-cytotoxic folate and an antibody or antibody fragment while the reference of Wedeking et al. was used to teach for the method for targeting a gadolinium-folate (folic acid)-antibody conjugate to a cell states as Wedeking et al. states that folate analogues may be used.

26. Applicant asserts that there is no disclosure in Niswender of folic acid conjugates for a therapeutic purpose.

27. The combined disclosures of Niswender, Wedeking et al. and Goldenberg et al. teach of gadolinium-folate (folic acid)-antibody conjugate for the method of selectively targeting diagnostic and therapeutic agents to multidrug resistant cells.

28. In regards to the nonstatutory obviousness-type double patenting.

29. Applicant asserts that the antibodies of 6,740,304 are inert and do not provide any targeting effect.

30. The antibodies of 6,740,304 encompass those of the instant claims (i.e. IgG) and therefore should have the same properties, such as having affinity for said tumor associated antigen and be capable of the same functions. Although applicant asserts that the antibodies of 6,740,304 do not provide the targeting effect there is no active step of explicitly targeting the antibody to the antigen.

Conclusion

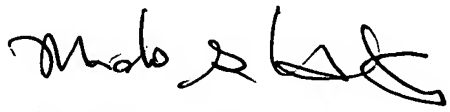
No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Perreira whose telephone number is 571-272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MP
November 15, 2007



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